

REMARKS

Applicants submit this Preliminary Amendment to address the issues raised in the Office Action mailed August 27, 2002. A response was timely filed on February 26, 2003, but in an Advisory Action dated March 25, 2003, the Examiner indicated that the amendment had not been entered. Claims 1-37 are pending in the application. Claims 10-13 and 15-37 have been withdrawn from consideration as being directed to a non-elected invention. Therefore, claims 1-9 and 14 are currently being examined. Claims 1-3 and 14 have been amended as discussed below and no new matter is added. The specific grounds of rejection are addressed below.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1-9 and 14 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. More specifically, the Action asserts that claims 1-3 are indefinite for reciting the term "about." Without acquiescing to the ground of rejection, applicants have amended claims 1-3 and 14, which no longer recite the term "about." Claims 1 and 3 have also been amended to add the term "amino acid" before the recitations of specific numbered amino acid residues in these claims. As applicants submit that the meaning of the numbered positions was clear in reference to the recited polypeptide sequence (SEQ ID NO:4), no new matter is added by this amendment.

In view of the above remarks, applicants submit that the grounds of rejection under 35 U.S.C. § 112, second paragraph, have been overcome. Accordingly, withdrawal of these rejections is respectfully requested.

Rejections under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 1-9 and 14 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly being non-enabled. In view of the amendment to claims 1, 3 and 14, applicants submit that the ground of rejection may be withdrawn to the extent that it applies to the "about" claim language. Regarding the 90% identity language, applicants traverse the rejection on the grounds that it would not require undue experimentation for one of skill in the art to determine if a

nucleic acid at least 90% identical to a claimed polynucleotide encodes a polypeptide that shares the biological activity of the polypeptide encoded by the polynucleotide of SEQ ID NO:3. Example 3 of the application discloses that EGFH2 is a secreted protein. mRNA encoding EGFH2 was injected into *Xenopus* oocytes and induced meiotic maturation via germinal vesicle breakdown. One of ordinary skill in the art can construct nucleic acid molecules corresponding to EGFH2 mRNA that is at least 90% identical to a polynucleotide encoding SEQ ID NO:4, or to a polynucleotide of SEQ ID NO:3. These mRNA molecules can be tested in the *Xenopus* oocyte system as described in Example 3 and the biological activity can be determined.

The Examiner states that the specification fails to provide guidance as to the "core structure" of SEQ ID NO:4 that is essential for maintaining the mitogenic activity. Applicants submit that the issue is whether undue experimentation would be required for one of skill in the art to construct or obtain a polynucleotide according to the claims, and to test it for the biological activity. Analysis of the actual structure is not a required element.

To further support the enablement of the claims, applicants submit herewith a Declaration under 37 C.F.R. § 132 by Dr. Judith Abraham, who has expertise and experience in this area of protein chemistry and activity, as evidenced by her current position as Research Director at Chiron Corporation, and her numerous scientific publications in peer-reviewed journals. Dr. Abraham discusses the fact that EGFH2 of the invention is also known as NRG4, and as such is known to signal through an ErbB receptor. (The relationship between EGFH2 and proteins of the NRG family is discussed in the specification at page 7, lines 3-16.) For NRG4 (EGFH2), the receptor is ErbB4. Several assays are available for determining if a protein falls within the scope of the claims. These assays are described in detail in paragraphs 6, 7, 8 and 9 of the Declaration. In each case, the results of the assay will provide a definite answer to allow one of ordinary skill in the art to determine if a protein falls within the scope of the claims. These routine assays are in some cases referred to in the specification, or are based on methods and reagents disclosed in the specification and/or well-known to those of skill in the art at the time of filing. In the context of the presently pending claims, the *Xenopus* oocyte assay is the designated assay for determining biological activity of a variant polypeptide.

In view of the above remarks and Dr. Abraham's declaration, applicants submit that the grounds of rejection under 35 U.S.C. § 112, first paragraph, have been overcome. Withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 1-9 and 14 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking an adequate written description. The Examiner states that "one of ordinary skill in the art cannot envision all of the nucleic acid and amino acid substitutions encompassed by the breadth of the claims or all of the isolated nucleic acid molecule that encode from about 1 to about 115 of SEQ ID NO:4 or from about 2 to about 115 of SEQ ID NO:4 and having mitogenic activity." (Office Action at page 5, second full paragraph.)

Without acquiescing to the ground of rejection, and to further the prosecution of the application, the term "about" is not recited in claims 1-3 and 14 as amended. Regarding the alleged lack of written description, applicants submit that the claims meet the requirements as described by the Examiner. Specifically, the specification and claims recite structural features common to the genus: at page 18, beginning at line 15, the specification specifically describes naturally occurring variants of SEQ ID NO:4, as well as the production of non-naturally occurring variants. The variants have amino acid sequences *at least 85%, 90%, or 95%* identical to the amino acid sequence of SEQ ID NO:4 (page 18, line 26 – page 19, line 1). In all cases, the properties and functions of the variants "are of the same type as a protein comprising the amino acid sequence encoded by the nucleotide sequence shown in" SEQ ID NO:3 (page 20, lines 16-18). Thus, the variants and the polypeptide of SEQ ID NO:4 share the *structural features* of a protein having the amino acid sequence of SEQ ID NO:4, in that the structure dictates the activity as measured using the methods as described and claimed (mitogenic activity as determined by *Xenopus* oocyte maturation assay).

Claim 14 has been amended herein to recite that the polynucleotide encodes a polypeptide comprising an amino acid sequence at least 90% identical to amino acids 4 to 50 of SEQ ID NO:4. These sequences represent the receptor domain, as described in the specification at page 13, line 29, to page 14, line 3. Thus, sequences within this group share a structural

feature common to the genus, specifically, receptor binding. As indicated in the Declaration of Dr. Judy Abraham, filed herewith, a receptor for EGFH2 has been identified as ErbB4 (Declaration at paragraphs 5 and 6). Thus, the polypeptides encoded by the polynucleotides of claim 14 share the structural feature of binding to ErbB4.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection under 35 U.S.C. § 112, Second Paragraph (Indefiniteness)

Claims 1, 3-9 and 14 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Examiner stated that (A) it was unclear how an amino acid sequence with 1 or 2 amino acids could have mitogenic activity, and (B) it was not clear whether the claims indicate the number of amino acids or the positions of the amino acids. It is clear from the context of the present specification that the language refers to position, and not to the number of amino acids. See, for example, page 13, lines 18-22, which indicates that the fragments consist of amino acids from, for example, “about 9” to “about 45.” If the language meant the number of amino acids, it would be so indicated: such as, “consists of 9 amino acids.” The alleged indefiniteness as it pertains to an amino acid sequence of 1 or 2 amino acids having mitogenic activity is moot in view of the correct interpretation of the claims language, in which the number “1”, “2” etc. refers to position. However, to further the prosecution, applicants have amended claims 1, 3 and 14 to clearly indicate that the language refers to amino acid positions. Reconsideration and withdrawal of this ground of rejection are respectfully requested.

Rejection under 35 U.S.C. § 112, First Paragraph (New Matter)

Claims 1, 3-9 and 14 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter, on the grounds that the “mitogenic activity” of claims 1, 3 and 14 represents a departure from the specification and claims as originally filed. Without acquiescing to the ground of rejection, applicants have amended claims 1, 3 and 14 to indicate that mitogenic activity is measured using the *Xenopus* oocyte maturation assay. Regarding claim 3, the Examiner stated that the specification and claims as filed do not provide clear support for

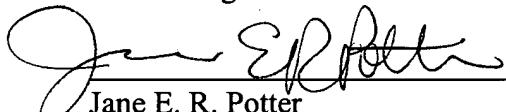
the nucleic acid molecule of claim 3 as amended. The mitogenic activity is disclosed at page 38, lines 15-23. The polynucleotides of the invention are disclosed at least at page 2, lines 1-15 and lines 19-26, and page 10, lines 13-24, which describes the biological activity to include mitogenic activity, and further provides that polynucleotides of the invention have equivalent biological activity. Reconsideration and withdrawal of this ground of rejection are respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made.**"

All of the pending claims in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 1-3, and 14 have been amended as follows:

1. (Twice amended) An isolated nucleic acid molecule comprising a polynucleotide selected from the group consisting of:
 - (a) a polynucleotide encoding a polypeptide comprising from [about] amino acid 1 to [about] amino acid 115 of SEQ ID NO:4;
 - (b) a polynucleotide encoding a polypeptide comprising from [about] amino acid 2 to [about] amino acid 115 of SEQ ID NO:4;
 - (c) a polynucleotide complement of the polynucleotide of (a) or (b), and
 - (d) a polynucleotide at least 90% identical to the polynucleotide of (a) or (b) wherein said polynucleotide encodes a polypeptide that has mitogenic activity as determined by Xenopus oocyte maturation assay.
2. (Twice amended) An isolated nucleic acid molecule comprising [about] 345 contiguous nucleotides from the coding region of SEQ ID NO:3.
3. (Twice amended) An isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide having an amino acid sequence from [about] amino acid 1 to [about] amino acid 115 or from [about] amino acid 2 to [about] amino acid 115 of SEQ ID NO:4, wherein said polypeptide has at least one conservative amino acid substitution at least 90% identity with SEQ ID NO:4, and mitogenic activity as determined by Xenopus oocyte maturation assay.
14. (Twice amended) A composition comprising an isolated polynucleotide encoding a polypeptide comprising an amino acid sequence selected from the group consisting of:
 - (a) an amino acid sequence from [about] amino acid 4 to [about] amino acid 50 of SEQ ID NO:4;

[(b) an amino acid sequence from amino acid 9 to amino acid 45 of SEQ ID NO:4;] and

[(c)] (b) an amino acid sequence at least [86%] 90% identical to said amino acid sequence of (a) [or (b)], wherein said polypeptide has mitogenic activity as determined by Xenopus oocyte maturation assay.